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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/652,282	08/30/00	GATELY M	9483

000151
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PATENT LAW DEPARTMENT
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HM12/0509

EXAMINER	
DIBRINO, M	

ART UNIT	PAPER NUMBER
1644	6

DATE MAILED: 05/09/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/652,282	Gately et al.
Examiner	**Art Unit**
Marianne DiBrino	1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Aug 30, 2000*

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-5, 14-20, 29, and 34-36* is/are pending in the applica

4a) Of the above, claim(s) *34-36* is/are withdrawn from considera

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-5, 14-20, and 29* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirem

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 4, filed 10/23/00

18) ☒ Interview Summary (PTO-413) Paper No(s). 5

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☒ Other: *Notice to Comply with the Sequence Rules*

DETAILED ACTION

1. Applicant's amendments, both filed 8/30/00, are acknowledged and have been entered.

Claims 1-5, 14-20, 29 and 34-36 are pending.

2. Restriction to one of the following inventions is required under 35 U.S.C. § 121:

I. Claims 1-5, 14-20 and 29 drawn to antibodies and a hybridoma, classified in Class 530, subclasses 387.1 and 388.23, and Class 435, subclass 346.

II. Claim 34, drawn to a method for producing polyclonal antibodies, classified in Class 514, subclass 2.

III. Claims 35 and 36, drawn to a method for producing a monoclonal antibody, classified in Class 435, subclass 70.21.

3. Invention I and II are related as process of making and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make other and materially different product or (2) that the product as claimed can be made by another and materially different process (M.P.E.P. § 806.05(f)).

In the instant case, the antibodies may be made by recombinant DNA techniques.

4. Invention I and III are related as process of making and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make other and materially different product or (2) that the product as claimed can be made by another and materially different process (M.P.E.P. § 806.05(f)).

In the instant case, the antibodies may be made by recombinant DNA techniques.

5. Inventions II and III are different methods.

These inventions require different ingredients and process steps to accomplish making polyclonal antibodies or a monoclonal antibody. For example, the method of Group II involves the step of obtaining antibodies from an immunized animal and screening the said antibodies, whereas the method of Group III involves harvesting antibody producing cells from an immunized animal, producing a hybridoma, and then screening hybridoma supernatents for antibodies specific for the desired epitope of the immunizing antigen.

Therefore they are patentably distinct.

6. Because these inventions are distinct for the reasons given above and the search required for any group from Groups I-III is not required for any other group from Groups I-III and Groups I-III have acquired a separate status in the art as shown by their different classification and divergent subject matter, restriction for examination purposes as indicated is proper.

7. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

8. During a telephone conversation with Mr. William Epstein on 5/4/01, a provisional election was made to select the Invention of Group I. Affirmation of this election must be made by Applicant in responding to this Office Action.

9. Accordingly, claims 34-36 (non-elected groups II and III) are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions.

10. Claims 1-5, 14-20 and 29 are presently being examined.

11. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reasons set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures and as follows:

This application fails to comply with *37 C.F.R. 1.821-1.825* because there was no submission of a Sequence Listing. Applicant required to either submit a new CRF and Sequence Listing or a letter authorizing the use of the sequence listing filed with the prior application, along with a statement that the sequences in the two cases are identical.

37 C.F.R. 1.821 (e) A copy of the "Sequence Listing" referred to in paragraph © of this section must also be submitted in computer readable form in accordance with the requirements of § 1.824. The computer readable form is a copy of the "Sequence Listing" and will not necessarily be retained as part of the patent application file. If the computer readable form of a new application is to be identical with the computer readable form of another application of the applicant on file in the Office, reference may be made to the other application and computer readable form in lieu of filing a duplicate computer readable form in the new application. The new application shall be accompanied by a letter making such reference to the other application

and computer readable form, both of which shall be completely identified.

(f) In addition to the paper copy required by paragraph © of this section and the computer readable form required by paragraph (e) of this section, a statement that the content of the paper and computer readable copies are the same must be submitted with the computer readable form. Such a statement must be a verified statement if made by a person not registered to practice before the Office.

12. Applicant is required under 37 C.F.R. 1.821(d) to amend the specification to list the appropriate SEQ ID NOS for sequences disclosed in the specification (for example, in the Brief Description of the Drawings for Figures 6 and 7).

13. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claims 1-5, 14-20 and 29 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1, 14 and 29 are indefinite in the recitation of "immunologically reacts with" in line 3, because the characteristics of the phrase "immunologically reacts with" are not defined in the specification, and this term has no art recognized meaning. The language is vague and indefinite because it is unclear what "immunologically reacts with" means.

b. Claim 20 as recited has no antecedent basis in base claim 19. The antibody recited in claim 19 is secreted by a hybridoma.

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

16. Claims 1-5, 14-20 and 29 are rejected under 35 U.S.C. 102(b) as being anticipated by Presky et al (of record, IDS #C15) as evidenced by Gately et al (U.S. Patent No. 5,780,597, of record) and by admissions in the specification (Figure 4).

~~Presky~~ et al teach antibodies, both polyclonal and monoclonal, to the human IL-12p75 heterodimer which consists of a p35 subunit and a p40 subunit wherein said antibodies bind to p75 and p35, but not to p40 (especially column 6, lines 6-10, column 42, lines 24-32, 44-46 and 50-58, column 44, lines 42-50). ~~Presky~~ et al also teach that antibodies to IL-12 may be humanized and used as therapeutic drugs (especially column 4, lines 9-13). Presky et al teach a heterodimer-specific humanized monoclonal antibody produced from a murine cell line, 20C2, that reacts with IL-12 and not p40 (page 31) and the hybridoma which makes such an antibody. The hybridoma producing said antibody does not encode the gene for human p35 or p40. It is an inherent property of said antibody that it reacts with the p35 subunit of p75 (column 44 at line 47) and not the p40 subunit (see Gately et al). It is an inherent property of 20C2 that it exhibit cross-reactivity with rhesus monkey IL-12 at higher concentrations as is evidenced by Figure 4 of the instant application. Presky et al also teach that the antibody completely blocked binding of human IL-12 to human IL-12Rb2, i.e., it "neutralizes at least about 90% of the bioactivity of human IL-12" as recited in instant claim 14 (especially page 392, Summary).The recitation of a method wherein the claimed antibody is made carries no patentable weight in this product claim. With regard to the properties of the antibody recited instant claims 15-17, the antibody has the specificity of such an antibody, and the functional properties are considered inherent properties of the reference antibody. The claimed molecule appears to be the same as the art absent a showing of any differences. Since the Patent Office does not have the facilities for examining and comparing the molecule of the instant invention to those of the prior art, the burden is on applicant to show an unobvious distinction between the molecule of the instant invention and that of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

17. Claims 1-4 are rejected under 35 U.S.C. 102(b) as being anticipated by Cytokine Bulletin (Genzyme, pages 1-13, Spring 1996).

The Cytokine Bulletin teaches a heterodimer-specific monoclonal antibody that reacts with IL-12 and not the p40 subunit of IL-12 (page 2). The Cytokine Bulletin further teaches neutralization of human IL-12 bioactivity by inhibiting IL-12 stimulated PHA-activated T-lymphoblasts (proliferation) using the said monoclonal antibody (page 2). The recitation of a process wherein the claimed antibody in single molecule form is produced carries no patentable weight in this product claim.

The reference teachings anticipate the claimed invention.

18. Claims 14-17 and 19 are rejected under 35 U.S.C. 102(b) as anticipated by Cytokine Bulletin.

The Cytokine Bulletin teaches a monoclonal antibody to human IL-12 that binds the heterodimer IL-12, but not the p40 subunit of the IL-12 heterodimer (page 2). With regard to the properties of the antibody recited instant claims 15-17, i.e., the concentrations of antibody and human IL-12 and "by inhibiting PHA-activated human lymphoblast proliferation", and "by inhibiting IL-12 stimulated IFN-γ production", the antibody has the specificity of such an antibody, and the functional properties are considered inherent properties of the reference antibody. The claimed molecule appears to be the same as the art absent a showing of any differences. Since the Patent Office does not have the facilities for examining and comparing the antibody of the instant invention to those of the prior art, the burden is on applicant to show an unobvious distinction between the molecule of the instant invention and that of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

19. Claims 1-4 and 29 are rejected under 35 U.S.C. 102(e) as anticipated by Trinchieri et al (U.S. Patent No. 5,811,523, of record) as evidenced by Gately et al (U.S. Patent No. 5,780,597, of record) and Carter et al (IDS reference "C16").

Trinchieri et al teach an antibody which reacts with the human cytokine NKSF heterodimer (which appears to have the same sequence as IL-12 as evidenced by Gately et al), but is specific for the 35 kD subunit which has the same sequence as the sequence of the IL-12 35kD subunit (especially claims 1, 3, 4, 5, and 7 and Figures 1 and 2). It is an inherent property of said anti-human IL-12 antibody that it would cross react with rhesus monkey IL-12 to some extent as evidenced by Carter et al who teach cross-reactivity of antibodies to IL-12 with mouse IL-12 and human IL-12 (about 60%, especially page 367, second column, lines 6-8), said mouse IL-12 has a much lower degree of homology to human IL-12 than rhesus monkey IL-12 has to human IL-12. Trinchieri et al inherently teach both monoclonal and polyclonal antibodies because the antibody is a murine antibody or it is a human antibody, i.e., it is a polyclonal or monoclonal antibody produced in a mouse or from mouse antibody producing cells, or it is a human antibody which is produced, for example, in a transgenic non-human animal with transgenes for human immunoglobulin.

The reference teachings anticipate the claimed invention.

20. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

21. Claims 1, 5, 14, 18 and 20 are rejected under 35 U.S.C. 103(a) as being obvious over Cytokine Bulletin in view Bendig (Methods: A Companion to Methods in Enzymology Vol. 8: 83-93, 1995) and admissions in the specification on page 16, last paragraph.

The Cytokine Bulletin teaches a mouse anti-human IL-12 antibody that does not react with the p40 subunit of IL-12 (page 1, IL-12 antibody table).

The Cytokine Bulletin does not teach a humanized version of said antibody.

Bendig teaches that clinical results with rodent antibodies have been disappointing primarily because rodent antibodies are highly immunogenic in humans. Bendig further teach that to help overcome this problem, rodent antibodies have been partially and fully humanized. Bendig teaches reliable methods for humanization have been developed, and Bendig teaches the methods in general (especially Abstract).

The specification discloses that procedures for humanizing known murine antibodies are known in the art (e.g., page 16, last paragraph).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made a humanized version of the mouse antibody taught by the Cytokine Bulletin as taught by Bendig et al and as per the procedures of the admitted prior art.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this because Cytokine Bulletin teaches a mouse anti-human IL-12 antibody and because of the art recognized advantages of humanized antibodies, such as reduced immunogenicity when administered to humans, taught by Bendig.

22. Claims 1, 5, 14, 18 and 20 are rejected under 35 U.S.C. 103(a) as being obvious over Trinchieri et al (U.S. Patent No. 5,811,523, of record) in view of Gately et al (U.S. Patent No. 5,780,597, of record) in view Bendig (Methods: A Companion to Methods in Enzymology Vol. 8: 83-93, 1995) and admissions in the specification on page 16, last paragraph.

Trinchieri et al teach an antibody which reacts with the human cytokine NKSF heterodimer (which appears to have the same sequence as IL-12), but is specific for the 35 kD subunit which has the same sequence as the sequence of the IL-12 35kD subunit (especially claims 1, 3, 4, 5, and 7 and Figures 1 and 2). It is an inherent property of antibodies that they are monoclonal or polyclonal. It is an inherent property of said anti-human IL-12 antibody that it would cross react with rhesus monkey IL-12 to some extent.

Trinchieri et al do not teach a humanized version the the said antibody.

Gately et al teach the sequence of the IL-12 subunits (especially Figures 25 and 26).

Bendig teaches that clinical results with rodent antibodies have been disappointing primarily because rodent antibodies are highly immunogenic in humans. Bendig further teach that to help overcome this problem, rodent antibodies have been partially and fully humanized. Bendig teaches reliable methods for humanization have been developed, and Bendig teaches the methods in general (especially Abstract).

The specification discloses that procedures for humanizing known murine antibodies are known in the art (e.g., page 16, last paragraph).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made a humanized version, as taught by Bendig et al and as per the procedures of the admitted prior art, of the mouse antibody taught by the Trinchieri et al which appears to be directed against the sequence of IL-12 as taught by Gately et al.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this because Trinchieri et al teaches a mouse antibody against the human IL-12 taught by Gately et al, and because of the art recognized advantages of humanized antibodies, such as reduced immunogenicity when administered to humans, taught by Bendig.

23. Claim 29 is rejected under 35 U.S.C. 103(a) as being obvious over Cytokine Bulletin (Genzyme, pages 1-13, Spring 1996) in view of EP 0677533 A2 (1995).

The Cytokine Bulletin teaches a heterodimer-specific monoclonal antibody that reacts with IL-12 and not the p40 subunit of IL-12 (page 2). The Cytokine Bulletin further teaches neutralization of human IL-12 bioactivity by inhibiting IL-12 stimulated PHA-activated T-lymphoblasts (proliferation) using the said monoclonal antibody (page 2). The Cytokine Bulletin also teaches the usefulness of the said antibody in accurate measurement of IL-12 because the said antibody does not cross react with free p40 (especially pages 1 and 2). The Cytokine bulletin further teaches that IL-12 is involved in the modulation of Th1/Th2 cellular responses and in regulation of the development of systemic and organ-specific autoimmunity, and that IL-12 promotes the growth of NK and T cells and contributes to macrophage activation through the stimulation of IFN-γ synthesis (paragraph 1 on page 1). The recitation of a process wherein the claimed antibody in single molecule form is produced carries no patentable weight in this product claim.

The Cytokine Bulletin does not teach a hybridoma that produces the said antibody.

EP 0677533 A2 teaches a method of obtaining autologous monoclonal antibodies to self - antigens involving genetically engineering a host animal to it does not biosynthesize at least one epitope of the self antigen, i.e., "knock-out" mice (especially Abstract, column 8 at lines 30-37), and using standard standard monoclonal antibody generation techniques to produce hybridomas producing monoconal antibodies (column 8 at lines 38-52).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have produced a hybridoma as per the teachings of EP 0677533 A2 using a knock-out mouse host which produces an antibody with the specificity of the antibody taught by Cytokine Bulletin (including the functional limitations in instant claims 16 and 17) to be used in quantitation of IL-12 or for the study of modulation of Th1/Th2 cellular responses modulated by IL-12.

One of ordinary skill in the art would have been motivated to do this because the Cytokine Bulletin teaches that such an antibody has usefulness in accurate measurement of IL-12 and that IL-12 is involed in Th1/Th2 modulation and because EP 0677533 A2 teaches a method of obtaining hybridomas producing antibodies to self antigens such as IL-12 taught by the Cytokine Bulletin.

24. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

25. Claims 1-5, 14-20 and 29 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-23 of U.S. Patent No. 6,225,117. Although the conflicting claims are not identical, they are not patentably distinct from each other because the monoclonal antibodies and hybridomas of U.S. Patent No. 6,225,117 are encompassed by the claims of the instant application, and the said antibodies of U.S. Patent No. 6,225,117 have the same specificity and functional properties of the antibodies recited in the claims of the instant application, as is evidenced by the specification of U.S. Patent No. 6,225, 117.

26. No claim is allowed.

27. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware of in the specification.

28. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marianne DiBrino whose telephone number is (703) 308-0061. The examiner can normally be reached Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

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